DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

9 4 2427

WARNING LETTER

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

AUG 22 2003

Mr. Matthew Jenusaitis
General Manager
Boston Scientific Corporation
3574 Ruffin Road
San Diego, California 92123

Dear Mr. Jenusaitis:

The purpose of this letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your facility conducted by Mr. Allen F. Hall, an investigator with the FDA Los Angeles District Office, on February 18-28, 2003, and during inspections of several clinical investigators involved in two studies sponsored by your firm, Boston Scientific Corporation (formerly Boston Scientific/Interventional Technologies). We also request a response from you informing us of your corrective actions to these violations of your obligations as the sponsor of these clinical investigations.

These inspections provided FDA with information about Boston Scientific Corporation's activities as the sponsor of two clinical investigations: [redacted] and the [redacted] and whether the sponsor complied with applicable FDA regulations. The [redacted] used in these clinical investigations is a device as that term is defined under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

In addition, the inspections were conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemption (IDE), Premarket Approval Application (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of clinical investigations. The clinical investigations were conducted under IDE [redacted] and supported PMA [redacted] and [redacted]

Our review of the inspection report prepared by the Los Angeles District Office reveals violations of the requirements of Title 21, Code of Federal Regulations (CFR) Part 812 – Investigational Device Exemptions. At the conclusion of the inspection, Mr. Hall listed his findings on a Form FDA-483 "Inspectional Observations," and discussed these findings with you. We acknowledge receipt of your March 31, 2003, response to this

FDA-483 from Dr. Paul Mason, Director of Regulatory Affairs, and discuss this response further below.

Additionally, our review of the inspection reports from the inspections of [redacted], [redacted] and [redacted] revealed deviations from the study requirements. These physicians provided data to support [redacted]. The deviations were issued on Forms FDA-483, "Inspectional Observations," which were presented to and discussed with [redacted] on June 28, 2002, [redacted] on March 24, 2003, [redacted] on August 9, 2002, and February 6, 2003; and [redacted] on February 6, 2003. The extent and nature of the problems observed at the above-referenced clinical investigator sites inspected by FDA resulted, in part, from your firm's failure to adequately monitor and secure clinical compliance at these sites. The violations noted on the FDA-483s and resulting from our subsequent review of the inspection reports are summarized below.

1. Failure to secure the investigator's compliance with the investigational plan and applicable FDA regulations [21 CFR 812.46].

A sponsor who discovers that an investigator is not complying with the signed investigator agreement, the investigational plan, the requirements of applicable FDA regulation, or any conditions of approval imposed by FDA or the reviewing Institutional Review Board (IRB) must promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation [21 CFR 812.46].

Our reviews of the inspection reports have disclosed that, despite periodic clinical monitoring visits and reports from your firm's designated monitors to your firm and the respective clinical investigators documenting serious protocol deviations and regulatory noncompliance by the above-referenced clinical investigators, such violations were repeatedly committed at the sites during the clinical investigation. There were no records that would demonstrate that your firm obtained prompt correction and subsequent compliance by the clinical investigators in question, or that your firm terminated a clinical investigator's participation in the study to prevent the recurrence of serious protocol deviations or regulatory violations.

For example, at the clinical sites of [redacted] and [redacted] in the [redacted] Study, the monitors reported numerous instances where study procedures required by the approved investigational plan, including laboratory testing, were either not performed or were not consistently followed at scheduled examinations. There were no records to indicate prompt compliance by these participating clinical investigators or termination of their participation in the clinical investigation.

Likewise, your monitoring records of clinical site [redacted] and clinical site [redacted] in the [redacted] Study contained instances where the study procedures required by the approved investigational plan, including laboratory testing,

were either not performed or were not consistently followed at scheduled examinations. The monitor records for Site noted that two co-investigators, on different occasions, had implanted a subject with the investigational within another a protocol deviation. The records did not describe the resolution of these deviations. There were no records to indicate prompt compliance by these participating clinical investigators or termination of their participation in the clinical investigation.

Your monitoring records noted that (and used informed consent forms that did not contain all basic elements of informed consent, as required by 21 CFR 50.25. The consent forms did not mention all procedures to be followed in the Study and did not accurately describe the benefits of the clinical investigation. There were no records at your site to indicate that you ensured the investigators' prompt compliance with the requirements of 21 CFR Part 50 – Protection of Human Subjects, or that you terminated their participation in the clinical investigation.

2. Failure to ensure proper monitoring of the clinical investigation [21 CFR 812.40]

As the sponsor of a clinical investigation, you are responsible for ensuring proper monitoring of investigators' activities. Records collected during the February 2003 inspection of your facility revealed insufficient monitoring at several clinical sites during the and clinical investigations. Monitoring problems observed during FDA's inspection of your facility and records included the following:

Even though your monitor did not check the site device log during the March 13-14, 2001, site visit, in the visit report dated April 25, 2001, the monitor stated that the device accountability records at clinical site of the Study had been determined by the monitor to be accurate and complete. A subsequent monitoring report dated June 21, 2001 (site visit May 15-16, 2001) acknowledged discrepancies in the accountability records, and stated that the clinical investigator would send a copy of the site accountability records to the sponsor. FDA reviewed an excerpt of those site accountability records, sent from the clinical investigator to your firm by communication dated June 20, 2001. The site device accountability records for the device configuration did not contain all entries found in the sponsor records, even though the monitor visited the site frequently and reported checking the device log. The clinical investigator's device accountability record contained omissions, failing to account for the receipt of the devices as early as April 4, 2000, and failing to account for the use of the devices as early as May 9, 2000 – both well before the March 2001 visit when which the monitor reported that these same records were complete and accurate.

The monitor's Site Initiation Checklist dated July 26, 2001, for clinical site of the Study indicated that several start-up activities including the Site Authorization Checklist had been completed. The Site Authorization Checklist requires

verification of a signed investigator's agreement and IRB approval of the clinical investigation. However, the clinical investigator did not sign the agreement until August 13, 2001. The IRB did not approve the clinical investigation until August 17, 2001. The Site Authorization Checklist was not completed until August 20, 2001.

Likewise, the monitor's Site Initiation Checklist dated July 24, 2001, for site [redacted] of the [redacted] Study indicates that several start-up activities including the Site Authorization Checklist had been completed. The investigator's agreement was not completed until September 24, 2001. The IRB did not approve the clinical investigation until October 11, 2001. The Site Authorization Checklist was not completed until October 15, 2001. The Monitor Visit Log showed no site visit on July 24, 2001.

The monitor did not verify the documentation of adverse events involving subject [redacted] at [redacted] Site [redacted]. The subject had an emergency coronary artery bypass surgery – itself a serious adverse event – on December 5, 2001, and subsequently died, seven days after the procedure. Although the emergency surgery had already occurred, the monitor's report of a visit on December 11, 2001, stated that there were no serious adverse events (SAEs) and no unexpected device-related SAEs. In the report of the subsequent monitor visit on March 7-8, 2002, the monitor stated that all SAEs were appropriately captured and documented, but the Adverse Event Form collected by the monitor for subject [redacted] was incomplete, lacking a clinical investigator's signature and date when the record was reviewed. The monitor also did not mention the death of this subject in the report.

In addition, the monitoring records obtained during the FDA inspections of the clinical sites did not document all noncompliance found at the clinical sites. The findings of FDA audits are summarized below:

[redacted]

At the clinical site of [redacted], FDA audited the case histories of 117 subjects during the July 29-August 9, 2002, inspection. The inspection revealed that [redacted] failed to enroll these subjects according the eligibility requirements in the investigational plan. Some case histories were backdated. It was also noted that the informed consents used and signed by all 117 subjects did not disclose study duration and procedures described in investigational plan, as required by 21 CFR 50.25. Five subjects consented with an outdated form and two subjects consented after treatment with the investigational device, in violation of the requirements of 21 CFR part 50 and 21 CFR 812.100.

At the clinical site of [redacted] FDA audited the case histories of 65 subjects during an inspection on June 24-28, 2002. That inspection revealed that [redacted] failed to enroll subjects according to the eligibility requirements in the investigational plan. In addition, many subject case histories contained unexplained changes in the referenced vessel diameter value. His records contained numerous

instances where study procedures, including laboratory testing, were either not performed or were not consistently followed at scheduled examinations. [redacted] did not obtain a legally effective informed consent from each study subject. It was also noted that the informed consents used and signed by all 65 subjects at his site contain language not easily understandable by those subjects, and thus failed to satisfy the requirements of 21 CFR part 50 and 21 CFR 812.100.

[redacted]

At the clinical site of [redacted], FDA audited the case histories of 22 subjects during an inspection on March 12-24, 2003. His records contained numerous instances where study procedures, including laboratory testing, were either not performed or were not consistently followed at scheduled examinations.

At the clinical site of [redacted] FDA audited the case histories of 30 subjects during the inspection on January 27-February 6, 2003. [redacted] failed to follow the eligibility requirements in the investigational plan. His records contained numerous instances where study procedures, including laboratory testing, were either not performed or were not consistently followed at scheduled examinations. [redacted] study subjects also signed an informed consent that did not contain the basic elements required by 21 CFR 50.25.

At the clinical site of [redacted] FDA audited the case histories of 11 subjects during an inspection of this clinical investigator on January 30-February 6, 2003. His records contained numerous instances where study procedures, including laboratory testing, were either not performed or were not consistently followed at scheduled examinations. These subjects signed an informed consent that did not have the basic elements required by 21 CFR 50.25. Additionally, the consent appeared to waive the rights of the subject, release, or appear to release those conducting the study from liability for negligence, in violation of 21 CFR 50.20.

Based on the inspectional observations, FDA concludes that your firm failed to follow the monitoring procedures that were described in your IDE and PMA submissions. The inadequate monitoring at the clinical sites and the inadequate follow up by the sponsor contributed to the recurrent deviations at various study sites.

3. Failure to prepare and submit complete, accurate, and timely reports [21 CFR 812.150(b) (5)]

You failed to prepare and submit progress reports to all of the reviewing Institutional Review Boards in the [redacted] and [redacted] Studies, as required by 21 CFR 812.150(b)(5). In your annual progress report on the [redacted] Study, you also failed to notify FDA about the August 22, 2000, IRB suspension of [redacted]

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in these clinical studies. It is your responsibility as a sponsor to assure adherence to each requirement of the Act and all applicable federal regulations.

We acknowledge receipt of the March 31, 2003, response to the FDA-483 from Dr. Paul Mason, Director of Regulatory Affairs. We note that Dr. Mason acknowledged the observations, on your behalf, and included new monitoring procedures to improve clinical oversight. However, these written procedures require further revisions to more clearly define monitoring activities and responsibilities. Written procedures that address only general aspects may be subject to individual interpretation and, thus, not adequately ensure proper monitoring.

For example, the [redacted] and the [redacted] do not describe whether the monitor should verify all case histories and related documentation or only select a representative sample during the visit. If a sample is to be selected, the procedures do not state the size and composition of this sample. The procedures also should define what documentation will be maintained of telephone and electronic communication between the monitors and the clinical sites.

In addition, these procedures do not specify the actions to be taken by sponsor to ensure prompt compliance where monitoring reveals noncompliance, including the timeline for resolution of noncompliance, and measures to prevent continual noncompliance by participating clinical investigators. All problems indicated in the monitoring records should be followed to resolution. If the clinical monitor is unable to resolve the problem, the problem should be brought to the attention of the [redacted] or designee and the problem or cause of the problem quickly resolved. As cited above, under 21 CFR 812.46, sponsors must assure compliance by the participating investigators with all applicable regulations and procedures and, if the compliance cannot be achieved within a specified period, the sponsor must terminate the participation of investigators who are not in compliance.

Another area to consider when you revise your written procedures is developing procedures to describe your monitor selection and training process. Under 21 CFR 812.43(d), a sponsor must select monitors qualified by training and experience to monitor the clinical investigation.

Although not required, many sponsors have a clinical trial quality assurance unit to perform independent audits and data verifications of clinical monitors to determine compliance with their standard operating procedures and with FDA regulations. If you decide to use a quality assurance unit, the unit should be independent of, and separate from, the routine monitoring or quality control functions of the organization.

Please acknowledge receipt of this letter within **15 working days**, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in regulatory action without further notice.

A copy of this letter has been sent to the Food and Drug Administration, Los Angeles District Office, 19900 MacArthur Boulevard, Suite 300, Irvine, California 92612. We request that a copy of your response be sent to the Los Angeles District Office and to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 2098 Gaither Road, Rockville, Maryland 20850, Attention: Kevin M. Hopson, Consumer Safety Officer. If you have any questions or require additional time to respond, please call Mr. Hopson at (301) 594-4720, extension 128.

Sincerely yours,

Michael G. Marcarelli
for Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health